PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 888/PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/HU 03/00017	International filing date *(day/month/year)* 04.03.2003	Priority date *(day/month/year)* 06.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D451/04, C07D451/04		
Applicant SANOFI-SYNTHELABO		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.09.2003	07.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Allard, M Telephone No. +31 70 340-2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU 03/00017

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-41 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 23, 25 (both partly)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 23, 25 (both partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22, 24, 26-29
	No:	Claims	23, 25
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	-

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D01: WO 01 96295 A (NOVARTIS AG ET AL) 20 December 2001 (2001-12-20)

D02: WO 98 19998 A (NOVARTIS AG) 14 May 1998 (1998-05-14)

D03: AUGUSTYNS KJL ET AL: 'Pyrrolidides: synthesis and structure-activity relationship as inhibitors of dipeptidyl peptidase IV' EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 4, 1997, pages 301-309, XP004086653

D04: US-A-4 001 422 (DANILEWICZ JC ET AL) 4 January 1977 (1977-01-04)

D05: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242778 & J. MED. CHEM., vol. 36, no. 23, 1993, pages 3707-3720,

D06: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242779 & J. MED. CHEM., vol. 34, no. 2, 1991, pages 656-663,

D07: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242780 & J. MED. CHEM., vol. 17, 1974, page 739, 742

D08: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242781 & J. CHEM. SOC. PERKIN TRANS. 1, 1976, page 938

D09: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242782 & TETRAHEDRON LETT., vol. 40, no. 37, 1999, pages 6745-6748,

D10: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242783 & YAKUGAKU ZASSHI, vol. 71, 1951, page 1053, 1057

D11: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242784 & J. HETEROCYCL. CHEM., vol. 19, 1982, pages 485-488,

D12: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242785 & ARCH. PHARM., vol. 332, no. 11, 1999, pages 389-398,

D13: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242786 & TETRAHEDRON LETT., vol. 39, no. 20, 1998, pages 3121-3124,

D14: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242787 & CHEM. BER., vol. 74, 1941, page 1661

D15: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242788 & J. MED. CHEM., vol. 43, no. 11, 2000, pages 2087-2092,

D16: EP-A-0 156 433 (JANSSEN PHARMACEUTICAL N.V.) 2 October 1985 (1985-10-02)

D17: WO 99 65895 A (SANOFI-SYNTHELABO) 23 December 1999 (1999-12-23)

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

With regard to claims 23 and 25 it should be noted that the present international preliminary examination is limited to those parts which have been the subject-matter of a complete international search, i.e. to compounds (II) or (V) wherein R^1 has the meanings recited in claims 8-12.

Re Item IV
Lack of unity of invention

The present application concerns N-substituted 1-aminoacetyl-2- cyano-pyrrolidines, their use and preparation (claims 1-22, 29).

Furthermore, the application concerns amino intermediates (claims 23 and 25) useful as precursors of the structural amino part of the final products on the one hand, and pyrrolidino intermediates (claims 24 and 26-28) useful as precursors of the structural pyrrolidine part of the final products on the other hand.

In such a combination of intermediates unity is not considered as being present, see "Administrative Instructions under the PCT" S-03/1998, Annex B, Part 1, (g)(vi), in combination with Rules 13.2 and 13.1 PCT.

Following inventions have therefore be identified:

- **Invention 1**: N-substituted 1-aminoacetyl-2-cyano-pyrrolidines, their use and preparation, and their amino precursors (claims 1-23, 25, 29)

- **Invention 2**: Pyrrolidine precursors (claims 24, 26-28)

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

Invention 1

The subject-matter of claims 23 and 25 lacks novelty in the light of D01 (see page 34, example 2kk), D02 (see page 12, example 17, and page 14, example 66), D04 (see examples 2 and 4), D05-D15, D16 (see example 40), and D17 (see examples 7 and 8).

The subject-matter of claims 1-22 and 29 is not disclosed in the available prior art and is therefore novel.

Invention 2

The subject-matter of claims 24 and 26-28 is not disclosed in the available prior art and is therefore novel.

Inventive step (Article 33(3) PCT)

Invention 1

The subject-matter of claims 23 and 25 lacking novelty lacks necessarily an inventive step.

The subject-matter of claims 1-22 and partly 29 lacks also an inventive step for the following reasons:

D01, which is considered to represent the closest prior art, describes substituted 1-glycyl-2-cyanopyrrolidines useful as DPP-IV inhibitors. D02 discloses similar

compounds with the same activity.

In the light of the teachings of D01, the problem underlying and possibly solved by the present application (see description page 13, lines 11 and 12) can be seen in the provision of further DPP-IV inhibiting cyanopyrrolidines having the same level of biological activity.

To solve this problem, the present application proposes to replace in the compounds disclosed in D1 the 2-cyanopyrrolidine moiety by a 4-fluoro- or 4,4-difluoro-2-cyanopyrrolidine moiety.

It is however already known from D03 that 4-fluoro-pyrrolidines can constitute a building block for DPP-IV inhibitors of structure comparable to the structure of the compounds of the present application.

The solution proposed by the present application appears therefore to be an obvious measure in the design of further DPP-IV inhibitors with the same level of activity, which does not involve an inventive step.

It is noted that the very general statement at page 13, lines 11 and 12, of the present application is not convincing to demonstrate that the problem of providing derivatives with improved activity has indeed be solved by the application.

Invention 2

The structure of the intermediates of claims 24, 26-28 and partly 29 is imposed by the structure of the aimed end-products: in the absence of an inventive step for these end-products, such intermediates, and consequently the subject-matter of claims 24, 26-28 and partly 29, lack also an inventive step.

Industrial applicability (Article 33(4) PCT)

Invention 1 and invention 2

The compounds, compositions and processes of claims 1-29 can be used in the pharmaceutical industry.

The compounds of the general formula (I) according to our invention can be prepared by the alkylation of the primary amines of the general formula (II) – wherein the meanings of R^1 and B are the same as given above – with the chloroacetyl derivative of the general formula (III) – wherein the meanings of R^2 and R^3 are as given above– and, if desired, by transforming the resulting compounds into one of their salts or solvates (Scheme 1).

In the course of the alkylation the chloroacetyl derivatives of the general formula (III) are applied in excess, and the resulting hydrogen chloride is bound by various acid binding agents, preferably by a base, such as for instance triethylamine, potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 2-*terc*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine - bound to a resin (PBEMP) -, which is known as super base. The reaction is preferably performed at a temperature between 25 and 70 °C.

The primary amines of the general formula (II) are prepared in a two-step synthesis (Scheme 2). In the first step the starting cyclic secondary amine of the general formula (IV) –wherein the meaning of Y is hydrogen atom, acetyl, or *tert*-butoxycarbonyl group- are arylated, preferably with the aryl halogenides of the general formula (X), wherein the meaning of R^1 is the same as given above and X stands for halogen atom. Depending on the meaning of R^1 the arylation reaction can be carried out in polar, protic or aprotic solvents, between 25 and 150 °C, preferably in alcohols (ethanol, *n*-butanol, *n*-pentanol), or without solvent in microwave oven, using an acid binder, for instance the excess of the amine, or DBU.

For starting material the free amines or protected secondary amines of the general formula (IV) -known from the literature- are used, thus 4-acetaminopiperidine (B = formula (1), Y = $COCH_3$) (US-3225037);
4-*tert*-butoxycarbonylaminopiperidine (B = formula (1), Y = $COOC(CH_3)_3$) (J. Med. Chem. **1999,** *42,* 2706); 3-(S)-*tert*-butoxycarbonylaminopiperidine (B = formula (2)) and 3-(S)-*tert*-butoxycarbonylaminopyrrolidine (B = formula (3)) (Synth. Comm. **1998,** *28,* 3919) in the last two cases Y = $COOC(CH_3)_3$; tert-butyl 8-azabicyclo[3.2.1]-oct-3-yl-*exo*-carbamate (B=formula (4), tert-butyl 8-azabicyclo[3.2.1]-oct-3-yl-*endo*-carbamate (B=formula (5)) (J. Med. Chem **1991,** *34,* 656), tert-butyl 9-azabicyclo[3.3.1]-non-3-yl *exo*-carbamate (B=formula (6)) and tert-butyl 9-azabicyclo-[3.3.1]-non-3-yl-*endo*-carbamate (B=formula (7)), (J. Med. Chem **1993,** *36,* 3720)) (Y=$COOC(CH_3)_3$).

Examples

Example 1

(2*S*)-4,4-difluoro-1-(2-{[8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl]*exo*-amino}acetyl)-2-pyrrolidine carbonitrile

The meaning of R^1 is 2-pyrimidinyl group, B means a group of formula (4), R^2 and R^3 mean fluorine atom in general formula (I).

a.) *tert*-butyl 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate with (V) general formula - where R^1 is 2-pyrimidinyl, Y is $COOC(CH_3)_3$, B is (4) group

14,7 g of *tert*-butyl 8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (65 mmol) (J. Med. Chem. **1991,** *34,* 656) and 8,93 g of 2-chloropyrimidine (78 mmol) and 12,7 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (85 mmol) are dissolved in 230 ml of 1-pentanol and heated under reflux for 4 hours. The solvents are evapotared and the residue is dissolved in 250 ml of chloroform and washed with 2x300 ml of water, dried over Na_2SO_4, and purified by column chromatography using *n*-hexane-ethyl acetate-chloroform (1:1:1) as eluent to result in white crystals which are triturated with *n*-hexane. Yield: 13,25 g (67%). M.p.: 113-115°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.49 (t, 2H), 1.66-1.97 (m, 6H), 3.89 (br, 1H), 4.61 (d, 2H), 6.60 (t+br, 1+1H), 8.34 (d, 2H).

b.) 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine with (II) general formula – where R^1 and B are given in step 1a.)

13 g of *tert*-butyl 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (43 mmol) are dissolved in a mixture of 120 ml of trifluoroacetic acid and 120 ml of dichloromethane. The solution is stirred for 30 minutes and evapotared. The residue is dissolved in 50 ml of dichloromethane and evaporated. This method is repetead three times and the last organic solution is extracted with 100 ml of saturated aq. sodium carbonate solution. The layers are separated and the aqueous phase is washed with 4x50 ml of dichloromethane. The combined organic layers are dried over Na_2SO_4 and evaporated to result in a white powder which is triturated with *n*-hexane. Yield: 6,7 g (77%). M.p.: 56-59°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.29 (t, 2H), 1.64-1.98 (m, 6H), 3.19 (m, 1H), 4.58 (dd, 2H), 6.57 (t, 1H), 8,33 (d,2H).

c.) *tert*-butyl) (2*S*)-2-(aminocarbonyl)-4,4-difluoro-1-pyrrolidinecarboxylate of the general formula (VII) wherein R^2 and R^3 mean fluorine atom

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.34-2.52 (m, 1H) + 2.66-2.83(m, 1H)(3-CH_2), 4.07-4.29 (m, 2H, 5-CH_2), 4.40(qv, 2H, CH_2Cl), 4.71 (m, 1H, 2-CH), 7.17 (br, 1H,) + 7.42 (d, 1H)(NH_2).

f.) (2*S*)-1-(2-chloroacetyl)-4,4-difluoro-2-pyrrolidinecarbonitrile of the general formula (III) wherein R^2 and R^3 mean fluorine atoms

10.4 g (46 mmol) of (2*S*)-1-(2-chloroacetyl)-4,4-difluoro-2-pyrrolidine-carboxamide are dissolved in 230 ml of dichloromethane and 13 ml (140 mmol) of phosphorous oxychloride are added thereto. The mixture is heated for 24 hours (if there is remaining starting material then it is refluxed further). During the refluxing the solution will become pale yellow and sticky solid material is precipitated. The solution is poured into another pot and 50 g of potassium carbonate are added thereto. After stirring for an hour the solid salts are filtered out and the solution is evaporated. Pale yellow oil is received which is triturated with n-hexane. The received yellow crystals are collected and 70 ml of diethyl-ether are added. Thus impurities are dissolved and pure white solid crystalline product is obtained. Yield: 6.0 g (56%). M.p.: 86-87°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.76-2.98 (m, 2H, 3-CH_2), 3.92-4.26 (m, 2H, 5-CH_2), 4.46 (qv, 2H, CH_2Cl), 5.11 (m, 1H, 2-CH).

g.) (2*S*)-4,4-difluoro-1-(2-{[8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl]*exo*-amino}acetyl)-2-pyrrolidinecarbonitrile

6,13 g of 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine (30 mmol) and 5,74 g of (2*S*)-1-(2-chloroacetyl)-4,4-difluoro-2-pyrrolidinecarbo-nitrile (27,5 mmol) and 12,5 ml of triethylamine (90 mmol) are dissolved in 250 ml of dry acetonitrile and stirred at 70°C for 3 hours and then at room temperature overnight. Then the mixture was evaporated to give a brownish thick oil which is purified by column chromatography using chloroform-methanol (6:1) as the eluent to result in a solid product which is crystallized from abs. ethanol. Yield: 5,7 g (77%). M.p.: 162-163°C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.32 (td, 2H), 1.6-2.0 (m, 7H), 2.6-2.9 (m, 2H), 2.85 (tt, 1H), 3.0-3.5 (m, 2H), 3.97 (ddd, 1H), 4.13 (ddd, 1H), 4.61 (m,2H), 5.05 (dd, 1H), 6.60 (t, 1H), 8.35 (m, 2H).

Example 2

(2*S*,4*S*)-4-fluoro-1-(2-{[8-(2-pyrazinyl)-8-azabicyclo-[3.2.1]-oct-3-yl]*exo*-amino}acetyl)-2-pyrrolidinecarbonitrile dihydrochloride

In the general formula (I) R^1 means 2-pyrazinyl-group, B means a group of formula (4), R^2 means hydrogen atom and R^3 means fluorine atom.

a.) *tert*-butyl 8-(2-pyrazinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate with (V) general formula - where R^1 is 2-pyrazinyl, Y is $COOC(CH_3)_3$, B is (4) group

0,54 ml of chloropyrazine (6 mmol) and 1,13 g of *tert*-butyl 8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (6 mmol) 0,97 ml of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (6,5 mmol) are dissolved in 40 ml of 1-pentanol and heated under reflux for 50 hours. The solvents are evapotared, the residue is dissolved in 50 ml of chloroform, washed with 4x30 ml of water, dried over Na_2SO_4, and purified by column chromatography using *n*-hexane-ethyl acetate-chloroform (3:1:1) as eluent to result in white crystals which are triturated with *n*-hexane. Yield: 0,55 g (36 %). M.p.: 122-123 °C.
^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.34 (s, 9H); 1.44-1.66 (m; 2H), 1.67-1.99 (m, 6H), 3.88 (m, 1H), 4.56 (bs, 2H), 6.59 (d, 1H), 7.77 (d, 1H), 8.07 (dd, 1H), 8.17 (d, 1H).

b.) 8-(2-pyrazinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-amine with (II) general formula – where R^1 and B are given in step 2a.)

3,85 mg of *tert*-butyl 8-(2-pyrimidinyl)-8-azabicyclo[3.2.1]oct-3-yl-*exo*-carbamate (1,26 mmol) are dissolved in 20 ml of 12% ethanolic hydrochloric acid and the solution is stirred for 7 hours. 20 ml water is added to the formed suspension and the pH is made to 11 with aqueous potassium hydroxide. The layers are separated, the organic phase are dried, evaporated and purified by column chromatography using ethyl acetate – methanol – 25 % aqueous NH_3 solution (17:3:1) as eluent to result in a pale yellow oil. Yield is 167 mg (65%). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.29 (t, 2H), 1.62-1.83 (m, 4H), 1.84-2.00 (m, 2H), 3.12 (sp, 1H), 4.57 (dd, 2H), 7.74 (d, 1H), 8.05 (dd, 1H), 8.15 (d, 1H).

c.) *tert*-butyl (2*S*,4*S*)-2-(aminocarbonyl)-4-fluoro-1-pyrrolidinecarboxylate of the feneral formula (VII) wherein R^2 means hydrogen atom and R^3 means fluorine atom

1.63 g (7 mmol) of (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-fluoro-2-pyrrolidinecarboxylic acid (Tetraheron Lett. **1998,** *39,* 1169) are dissolved in 25 ml of dichloromethane and 1.2 ml (8.4 mmol) of triethylamine are added. 0.86 ml (7 mmol) of